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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/777,081	02/13/2004	Yoshiaki Yanai	YANAI=2A	4020

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EXAMINER

HISSONG, BRUCE D

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/777,081	Applicant(s) YANAI ET AL.	
	Examiner Bruce D. Hissong, Ph.D.	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>2/13/04, 4/11/05</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Formal Matters

1. The information disclosure statement received on 4/11/2005, and the contents of the application received on 2/13/2004, have been entered into the record.
2. Claims 1-18 are currently pending and are the subject of this Office Action.

Information Disclosure Statement

1. The information disclosure statement received on 2/13/2004 has been fully considered by the Examiner.
2. The information disclosure statement received on 4/11/2005 has been fully considered by the Examiner.

Claim Objections

1. The Examiner suggests the syntax of claims 5-7 can be improved by amending the claims to read "The expression enhancer of claim 1 wherein the protein synthesis inhibitory gene is selected from the group consisting of.....", instead of "as a protein synthesis inhibitory gene" as currently written.
2. The Examiner suggests the syntax of claim 12 can be improved by amending the claim to read "An expression enhancer for structural genes under the regulation of a transcription regulatory region selected from the group consisting of the transcription regulatory region of 2',5'-oligoadenylate synthetase, or double-stranded RNA-dependent protein kinase, said enhancer comprising IFN- α 2 and IFN- α 8 subtypes of IFN- α as active ingredients.....".

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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1. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the term "expression enhancer" are not defined by the specification or the claims. It is not clear if the claimed expression enhancer increases expression of protein synthesis inhibitory gene transcription, increases protein levels, increases activity of said proteins, or something else. Furthermore, it is not clear if the term represents a composition or a method; for the purpose of examination, the Examiner has interpreted the term "expression enhancer" to represent a composition.

2. Claim 2, as well as dependent claims 4 and 6, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites an "expression enhancer wherein at least 90% of the total IFN- α activity as expressed in international units.....". The claim does not define or limit the activity of the IFN- α , and thus it is not clear which IFN- α activity the claim is drawn to.

3. Claims 5-6 and 12, as well as dependent claims 10-11 and 14, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite an expression enhancer which is for a member of the group consisting of 2'5'-oligoadenylate synthetase (2'5'-OAS), double-stranded RNA-dependent protein kinase gene, and *mixtures thereof*. It is not clear if the expression enhancer is intended to enhance expression of several genes at once, enhance the expression of genes in a mixture/composition, or something else.

4. Claims 15-16, as well as dependent claims 17-18, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite an enhancer "for gene expression inducing action of protein synthesis inhibitor genes". The intended meaning of this phrase is not clear. Clarification is required. Additionally, claim 15 recites "an enhancer for gene expression inducing action.....by IFN- α 8 subtype of human IFN- α , comprising IFN- α 2 subtype of human IFN". Similarly, claim 16 recites "an enhancer for gene expression.....by IFN- α 2 subtype of human IFN- α , comprising IFN- α 8 subtype of human IFN". As written, the

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language of claims 15 and 16 is open-ended because the claimed expression enhancers *comprise* IFN- α 2 or IFN- α 8, respectively. It is not clear if the expression enhancer of claims 15 and 16 are intended to include only IFN- α 2, or only IFN- α 8, respectively, or if the claimed enhancers of both claims can include both IFN- α subtypes. Clarification is required.

5. Claims 3-4 and 8, as well as dependent claim 7, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite various activity ratios of an expression enhancer. It is not clear if the recited activity ratios are the ratio of IFN- α 2:IFN- α 8, or IFN- α 8:IFN- α 2.

6. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites a polysaccharide *consisting essentially of* a repeating unit of maltotriose. It is not clear if the term "consisting essentially of" is meant to mean "consisting of", "comprising", or something else. Thus, the metes and bounds of the term are not clear.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression enhancer for antiviral activity, said expression enhancer comprising interferon (IFN)- α polypeptides set forth in the examples, and defined by SEQ ID NO: 1 and SEQ ID NO:2, does not reasonably provide enablement for an expression enhancer comprised of any other IFN polypeptide, and does not reasonably provide enablement for an expression enhancer that enhances any other biological activity or protein. The specification does not enable any person skilled in the art to which it pertains, or with which

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it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of claims. *Ex Parte Forman*, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The breadth of the claims is excessive, because as written, the claims encompass an expression enhancer comprised of a number of possible IFN- α polypeptides. The specification, in paragraph 0011, pages 7-8, states that "The IFN- α 2 and IFN- α 8 subtypes as referred to as in the present invention should not be restricted to the amino acid sequences of SEQ ID NOs: 1 and 2 and may include those which have different amino acid residues from the amino acid sequence of SEQ ID NO: 1 or 2, usually, at positions not more than 10, preferably, not more than eight, and more preferably, not more than six in SEQ ID NO: 1 or 2." The specification, in paragraph 0012, page 8, further asserts that "Any subtypes can be used in the present invention independently of their origins and preparation methods as long as they are the IFN- α 2 and IFN- α 8 subtypes defined above."

There is no guidance or working examples in the specification that teaches that IFN- α polypeptides other than those of SEQ ID NOs 1 and 2 can be used to enhance any biological activity. As stated above, the specification teaches that the claimed expression enhancer can be comprised of polypeptides that exhibit less than 100% homology to the polypeptides of SEQ ID NOs 1 and 2. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. As an example of the unpredictable effects of mutations on protein function, Mickel *et al* (Med. Clin. North Am., 2000, Vol. 84(3), p. 597-607) teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR – p. 597). Several mutations can cause cystic fibrosis, including the G551D mutation. In this mutation, a glycine replaces the aspartic acid at position 551, giving rise to the cystic fibrosis phenotype. In the most common cystic fibrosis mutation, Δ -F508, a single phenylalanine is deleted at position 508, giving rise to the cystic fibrosis phenotype. Thus, even the substitution or deletion of a single amino acid can have

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dramatic and *unpredictable* effects on the function of the protein. In the instant case, the specification does not teach which amino acid residues of SEQ ID NOs 1 and 2 can be altered and retain the desired biological activity, and therefore a person of ordinary skill in the art would not be able to predict which of the many IFN- α 2 or IFN- α 8 polypeptides created by mutation of SEQ ID NOs 1 or 2 respectively, could be used commensurate in scope with the claims. Furthermore, the specification teaches that the IFNs of the claimed expression enhancer can be of any origin. The specification presents examples of IFN- α 2 and IFN- α 8 recombinantly produced in bacteria. However, it is well-known in the art that there are numerous differences in protein produced in bacteria vs. proteins produced in eukaryotic cells. For example, recombinant proteins from bacteria are not glycosylated, while those from eukaryotes are. The specification does not provide guidance or examples for using any glycosylated (i.e. non-bacterial in origin) IFNs in the claimed expression enhancer, and a person of ordinary skill in the art would not be able to predict if glycosylated IFNs could be used commensurate in scope with the claims.

The claims of the instant invention also recite an expression enhancer for protein synthesis inhibitory genes. Although several such genes are well-known in the art, and the specification also teaches the identities of several protein synthesis inhibitory genes, the specification does not teach, or provide examples, showing that any of these genes are enhanced in response to the claimed expression enhancer. The specification does provide guidance and examples showing that the anti-viral activity of tissue culture cell lines is enhanced in response to IFN- α 2 and IFN- α 8 in varying activity ratios, but this enhanced anti-viral activity is not correlated with any specific protein synthesis inhibitory genes. Because viral immunity is dependent on a number of genes, a person of ordinary skill in the art would not be able to predict which of the many possible protein synthesis inhibitory genes are enhanced in response to the claimed expression enhancer. Furthermore, claim 12 is drawn to enhancement of structural genes under the regulation of a transcription regulatory region selected from several protein synthesis inhibitory genes. There is no guidance or examples of any structural genes that can be enhanced by the claimed expression enhancer, nor any recitation of any transcriptional regulatory elements in any gene that would be useful in enhancing the expression of said structural genes. A skilled artisan would not be able to predict which of the many possible structural genes could be enhanced by the claimed expression enhancer, and

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furthermore, would not know which of the many possible transcriptional regulator regions would could be used commensurate in scope with the claims.

In summary, due to the excessive breadth of the claims, which read on an expression enhancer comprised of many possible IFN polypeptides and enhancing the expression of many possible protein synthesis inhibitory genes, the lack of guidance and examples in the specification showing that any polypeptide other than those of SEQ ID NOs 1 and 2 can be used to enhance any biological activity other than anti-viral activity in cell-lines, and the unpredictability inherent in the art regarding which of the many possible IFNs, from any source, that can be used, a person of ordinary skill in the art would require further, undue experimentation to make and use an expression enhancer comprised of any IFN- α 2 and IFN- α 8 polypeptide, other those of bacterially-produced SEQ ID NO:1 or 2, to enhance the expression of any protein synthesis inhibitory gene.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to an expression enhancer comprised of IFN- α 2 and IFN- α 8. As stated above in the 35 U.S.C. 112, first paragraph enablement rejection, the IFN- α polypeptides of the claimed expression enhancer can be defined by SEQ ID NOs 1 and 2, but may also include polypeptides with less than 100% identity to the polypeptides of SEQ ID NOs 1 or 2. There is no disclosure of any polypeptide with less than 100% identity to SEQ ID NOs 1 or 2 in the specification or claims of the instant invention. Therefore, the Applicants have not fully described the genus of polypeptides with less than 100% identity to SEQ ID NOs 1 or 2 that are still capable of functioning as an expression enhancer.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the

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claims is a requirement that the polypeptides have homology to SEQ ID NOs 1 or 2. There is no identification of any particular portion of the polypeptides of SEQ ID NOs 1 or 2 that must be conserved in order to maintain function. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 5-6, and 12-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Testa *et al* (US 5,503,828). The claims of the instant invention are drawn to an expression enhancer for protein synthesis inhibitor genes, with said expression enhancer comprising IFN- α 2 and IFN- α 8. Testa *et al* teaches a composition comprising of at least %50 of alleles of IFN- α 2 and IFN- α 8 (see claim 1). Testa *et al* also teaches a composition comprised of IFN- α 2 and IFN- α 8 in a pharmaceutically acceptable carrier (column 3, lines 19-26; column 12, lines 33-61). Thus, Testa *et al* anticipates the limitations of claims 1-2 and 13-14 of the instant application. In addition, because of the open-ended language of claims 15 and 16, which read on an expression enhancer *comprising* IFN- α 2 (claim 15), or IFN- α 8 (claim 16), Testa *et al* also meets the limitations of these claims as well. Finally, claims 5-6, 12, 17-18 recite an expression enhancer for protein synthesis inhibitory genes, including 2',5'-oligoadenylate synthetase and double-stranded RNA-dependent protein kinase. It has long been known in the art that Type I IFNs, such as IFN- α 2 and IFN- α 8, are potent inducers of these genes (De Maeyer *et al* – cited in the information disclosure statement received on 2/13/2004). Therefore, although Testa *et al* does not specifically teach an expression enhancer for 2',5'-oligoadenylate synthetase and double-stranded RNA-dependent protein kinase, the instant application is not patentably distinct from the teachings of Testa *et al* because any composition comprising IFN- α 2 and IFN- α 8 would inherently induce expression of these genes, and thus the composition of Testa *et al* meets the limitations of claims 5-6, 12, and 17-18 of the instant application.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Testa *et al*, in view of Xi *et al* (Pharm. Res., 1996, Vol. 13(12), p. 1846-1850). The claims of the instant application are drawn to an expression enhancer comprising IFN- α 2 and IFN- α 8, wherein the IFN subtypes have a water-soluble macromolecule covalently attached to the peptide chains of the subtypes. Claim 11 is further drawn to the attachment of a water-soluble macromolecule that consists essentially of a repeating unit of maltose.

Testa *et al* describes a composition comprised of the IFN subtypes IFN- α 2 and IFN- α 8 (see claim 1), but does not teach IFN subtypes attached to any water-soluble macromolecule. Xi *et al* teaches chemical/covalent conjugation of the water-soluble polysaccharide pullulan to IFN- α subtypes (see p 1846, 2nd column last paragraph). Pullulan is known in the art as a water-soluble polymer consisting of maltotriose subunits (see <http://en.wikipedia.org/wiki/Pullulan>). Xi *et al* also teaches that conjugation of pullulan to IFN- α targets the IFN to the liver, and pullulan-conjugated IFN- α induced 2',5'-oligoadenylate synthetase activity (see p. 1848).

Therefore, a person of ordinary skill in the art, at the time the instant invention was made, would be motivated to create an expression enhancer comprised of IFN- α 2 and IFN- α 8, with the IFN subtypes conjugated to a water-soluble macromolecule. The motivation to do so is provided by Testa *et al*, which describes a composition comprising IFN- α 2 and IFN- α 8, and Xi *et al*, which teaches a method of pullulan conjugation to IFN, and showing that the IFN-pullulan conjugate enhances a desired biological activity. One of ordinary skill in the art, therefore, would have both the motivation and a reasonable expectation of success, to create the expression enhancer of the instant application.

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Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D., can be reached at (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BDH
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ROBERT S. LANDSMAN, PH.D.
PRIMARY EXAMINER